## REMARKS

Telephone Interview:

Applicants express appreciation to Examiner Zeman for the courtesy extended to Applicants' agent, Angela Dallas Sebor, to inventor Dr. Geoffrey Pietersz, and to Applicants' representative, Ms. Vanessa Waddell, during the telephone interview of December 20, 2005. During the telephone interview, the outstanding issues under 35 U.S.C. § 112, first paragraph (enablement) and 35 U.S.C. § 103 were discussed. With regard to the enablement rejection, possible claim amendments were discussed that would potentially remove the rejection, including limiting the claims to mannose receptor-bearing antigen presenting cells, and clarifying that the cells are pulsed with the conjugate *ex vivo* or *in vitro*. In addition, the possibility of providing a third party expert opinion in the form of a Declaration under 37 CFR 1.132 that confirms that the invention can be made and used as claimed was discussed. With regard to the rejections under § 103, Applicants' agent explained that evidence would be provided that the reference of Koning et al. is not available as prior art, and arguments against the combination of McKenzie et al. and Marakovsky et al. were discussed.

Claim Amendments:

The prior claims have been cancelled and presented as new claims to facilitate the Examiner's review of the claims and present all dependent claims in a proper order with respect to independent claims. Support for the new claims is found in the specification and prior claims as follows.

Support for Claim 73 is found in original and prior Claim 1. Additional support for the recitation of antigen presenting cells as the mannose receptor bearing cell is found, for example, on page 16, lines 1-23. Support for the recitation of pulsing the cells *ex vivo* or *in vitro* with the conjugate is found, for example, on page 15, lines 12-17; page 42, lines 21; page 44, lines 3-5; page 45, line 20 to page 46, line 12; page 47, lines 15-16.

Support for Claim 74 is found in original and prior Claim 3.

Support for Claims 75 and 89 is found in is found in original and prior Claim 4.

Support for Claim 76 is found in original and prior Claim 5.

Support for Claim 77 is found in original and prior Claims 8 and 10.

Support for Claim 78 is found in original and prior Claim 9.

Support for Claims 79 and 88 is found in original and prior Claim 11.

Support for Claims 80 and 90 is found in original and prior Claim 13.

Support for Claim 81 is found in original and prior Claim 14.

Support for Claim 82 is found in original and prior Claim 15.

Support for Claim 83 is found in original and prior Claim 15.

Support for Claim 84 is found in original and prior Claim 17.

Support for Claim 85 is found in original and prior Claim 19.

Support for Claim 86 is found in original and prior Claim 20. Additional support for the recitation of antigen presenting cells as the mannose receptor bearing cell is found, for example, on page 16, lines 1-23. Support for the recitation of pulsing the cells *ex vivo* or *in vitro* with the conjugate is found, for example, on page 15, lines 12-17; page 42, lines 21; page 44, lines 3-5; page 45, line 20 to page 46, line 12; page 47, lines 15-16, and generally in Example 1.

Support for Claim 87 is found in original and prior Claim 20. Additional support for the recitation of antigen presenting cells as the mannose receptor bearing cell is found, for example, on page 16, lines 1-23. Support for the biological response modifier being selected from cytokines and vitamins is found in original and prior Claim 10. Support for the recitation of pulsing the cells *ex vivo* or *in vitro* with the conjugate is found, for example, on page 15, lines 12-17; page 42, lines 21; page 44, lines 3-5; page 45, line 20 to page 46, line 12; page 47, lines 15-16, and generally in Examples 1.

Objection to the Specification and Rejection of Claims 1, 3, 5-11, 13-17, 19-21, 24-26, 38 and 70 Under 35 U.S.C. § 112, First Paragraph:

The Examiner has objected to the specification and rejected Claims 1, 3, 5-11, 13-17, 19-21, 24-26, 38 and 70 under 35 U.S.C. § 112, first paragraph, on the basis of enablement. Specifically, while the Examiner acknowledges that the specification is enabling for immunoregulatory compositions comprising mannose receptor bearing antigen presenting cells (APCs) and a conjugate comprising MUC1 or CRIPTO and the recited carbohydrate polymer comprising mannose, the Examiner contends that the specification does not enable cells other than APCs or antigens other than MUC1 or CRIPTO. The Examiner asserts that people of skill in the art require documented

evidence that a benefit can be derived by the therapeutic application of a given substance, but contends that the specification provides no evidence what other conjugates would elicit the requisite immune response. Furthermore, the Examiner contends that the specification provides no guidance with regard to the use of cells other than APCs.

Applicants traverse the rejection of Claims 1, 3, 5-11, 13-17, 19-21, 24-26, 38 and 70 under 35 U.S.C. § 112, first paragraph. Initially, as discussed with the Examiner in the December 20 interview, the claims have been amended to limit the claims to mannose receptor bearing cells that are antigen presenting cells. Therefore, this aspect of the enablement rejection is believed to be moot.

With regard to the issue of whether the specification enables the recitation of any tumor antigen in the conjugate, Applicants have the following reply. First, as discussed with the Examiner in the December 20 interview, contrary to the Examiner's apparent position that predictable therapeutic benefit of the claimed invention relies on the tumor antigen, Applicants submit that the choice of antigen to be used in the conjugate does not influence affect of the conjugate on the mannose receptor-bearing APCs - the science behind the action of the conjugate on the APCs explains this effect. Specifically, the present inventors have discovered that the oxidized mannan-polymer portion of the conjugate, which targets the antigen (*i.e.*, any antigen) to the mannose receptor-bearing APCs, induces maturation of the APCs and causes the antigen to be processed by class I pathway in APCs, in addition to processing of the antigen through class II pathways that might normally be expected. Therefore, the conjugate will have this effect on an APC regardless of which antigen is provided in the conjugate. The immunogenicity of the selected antigen, therefore, is enhanced by its provision in the claimed conjugate and furthermore, by the administration of the conjugate to the recited mannose receptor-bearing APCs. It was quite surprising that the conjugate, due to the oxidized carbohydrate polymer comprising mannose, channeled the antigen into the class I pathway, which provides a great therapeutic benefit in that CTL responses ($CD8^+$ T cell responses) can be generated against the antigen. It was also quite surprising that the conjugate, again due to the oxidized carbohydrate polymer comprising mannose, actually caused the *maturation* of the APC, whereas typically, APCs must be activated or matured using other factors (*e.g.*, cytokines). Therefore, the immunogenicity of any antigen against which an immune response can be generated

is readily enhanced by the use of the antigen in the claimed composition. As such, one could consider the delivery of the antigen to the APC via the conjugate to provide an "adjuvant effect", and accordingly, one may select any tumor antigen against which an immune response is desired and use the claimed composition to elicit an enhanced cellular immune response against the antigen, including a $CD8^+$ (CTL) response, which is highly desirable in the case of generating an immune response against a tumor antigen. The exemplified tumor antigens only illustrate the efficacy of the presently claimed invention, and it is submitted that the invention is not limited to MUC1 or CRIPTO.

In further support of Applicants' position on this point, enclosed is a Declaration under 37 CFR 1.132 of Dr. Chris Schmidt. Dr. Schmidt provides an independent, third party opinion that, given the guidance and evidence of the invention provided by the present specification, one of skill in the art would readily be able to make and use the present invention as claimed, with respect to any tumor antigen. Specifically, the Declaration of Dr. Schmidt concludes that, given the guidance provided in the specification and the general knowledge of those of skill in the art, one would be able to make and use a composition as claimed using any tumor antigen.

During the December 20 interview, the Examiner appeared to be at least partially persuaded with regard to Applicants' position on enablement as set forth above. One concern expressed by the Examiner in the December 20 interview was whether, in the claimed composition, the mannose receptor bearing APCs are actually pulsed with the antigen conjugate. The Examiner suggested that clarification of this point by amendment of the claims would be more reflective of Applicants' position that the conjugate expands and enhances the immune response to antigen via its effect on the APCs. Accordingly, the claims have been amended to adopt the Examiner's suggsestion and to clarify that the APCs have been pulsed with the antigen conjugate *in vitro* or *ex vivo*.

In view of the foregoing remarks and discussion, the Examiner is respectfully requested to withdraw the rejection of Claims 1, 3, 5-11, 13-17, 19-21, 24-26, 38 and 70 under 35 U.S.C. § 112, first paragraph.

Rejection of Claims 1, 3-11, 13-17, 19-21, 24-26, 38 and 70 Under 35 U.S.C. § 103:

The Examiner has rejected Claims 1, 3-11, 13-17, 19-21, 24-26, 38 and 70 under 35 U.S.C. § 103, contending that these claims are unpatentable over McKenzie et al. (EP 0 659 768) in view of Koning et al. (WO 98/13378). Specifically, the Examiner initially contends that the limitation of immunoregulatory compositions comprising mannose receptor bearing cells was not disclosed or enabled in the parent application and therefore, submits that the filing date of the instant application determines the availability of art under 35 U.S.C. § 103. With regard to the cited combination of references, the Examiner contends that McKenzie et al. disclose a conjugate comprising a tumor antigen (mucin) and a carbohydrate polymer (mannose) that is used to induce cell-mediated responses. The Examiner admits that McKenzie et al. differ from the instant claims in that the conjugate is not combined with mannose receptor bearing cells at the time of administration to the patient or used for *ex vivo* pulsing. The Examiner asserts that Koning et al. teach mannosylated antigens to enhance the uptake and MHC restricted presentation of antigens by mannose-receptor bearing cells, and further contends that it would have been obvious to combine the conjugate of McKenzie et al. with the cells of Koning et al. to increase the uptake efficiency of an antigen.

Applicants traverse the rejection of Claims 1, 3-11, 13-17, 19-21, 24-26, 38 and 70 under 35 U.S.C. § 103. Initially, Applicants respectfully refer the Examiner to the priority claim of the present application to U.S. Provisional Application No. 60/060,594, filed September 29, 1997. This provisional application fully discloses the present invention as claimed, including the pulsing of mannose receptor-bearing antigen presenting cells with a conjugate comprising a tumor antigen and the recited oxidized carbohydrate polymer comprising mannose (See, for example, page 5, line 15 to page 8, line 2; and page 12, lines 5-23; and the Examples). Therefore, the instant claims are, at a minimum, entitled to a priority date of September 27, 1997 for the full scope of the claimed invention.

With regard to the combination of McKenzie et al. and Koning et al., Applicants submit that Koning et al. is not available as prior art against the instant claims. Koning et al. is a PCT publication that published on April 2, 1998. Koning et al. was filed on September 25, 1997, which is not on or after November 29, 2000, and therefore, Koning et al. is only available as prior art as of its publication date. Given that the present claims are entitled to a priority date of September 27,

1997, Koning et al. is not available as prior art. McKenzie et al., as the Examiner acknowledges, does not teach combining a conjugate with mannose receptor bearing cells at the time of administration to the patient or in *ex vivo* pulsing. Moreover, there is no suggestion in McKenzie et al. of using mannose receptor bearing cells as claimed, and therefore, there can be no teaching or suggestion in McKenzie et al. of the advantages achieved by the presently claimed invention. Therefore, McKenzie et al. fails to teach each and every element of the claimed invention, and fails to suggest the claimed invention.

In view of the foregoing discussion, the Examiner is respectfully requested to withdraw the rejection of Claims 1, 3-11, 13-17, 19-21, 24-26, 38 and 70 under 35 U.S.C. § 103.

Rejection of Claims 1, 3-11, 13-17, 19-21, 24-26, 38 and 70 under 35 U.S.C. § 103:

The Examiner has rejected to Claims 1, 3-11, 13-17, 19-21, 24-26, 38 and 70 under 35 U.S.C. § 103, contending that these claims are unpatentable over McKenzie et al. (EP 0 659 768) in view of Marakovsky et al. Again, the Examiner initially asserts that the instant filing date determines the availability of references as prior art. With regard to the cited combination of references, the reasons for the citation of McKenzie et al. are reiterated as in the rejection in view of McKenzie et al. and Koning et al. discussed above. The Examiner contends that Marakovsky et al. teach the use of antigen expressing, activated mannose receptor bearing cells (dendritic cells) to present tumor antigens to T cells, the use of cytokines in combination with the cells, and methods of inducing immune responses utilizing antigen-pulsed dendritic cells. Therefore, the Examiner contends that it would have been obvious to combine the antigen-mannose conjugate of McKenzie et al. with the activated dendritic cells of Marakovsky et al., in order to take advantage of the dendritic cells to increase the immunogenicity of antigens.

Applicants traverse the rejection of Claims 1, 3-11, 13-17, 19-21, 24-26, 38 and 70 under 35 U.S.C. § 103. First, as discussed above, Applicants submit that the instant claims are, at a minimum, entitled to a priority date of September 27, 1997 for the full scope of the claimed invention.

The Examiner argues that it would have been obvious to combine the antigen-mannose conjugate of McKenzie et al. with the activated dendritic cells of Marakovsky et al., in order to take advantage of the dendritic cells to *increase the immunogenicity of the antigen conjugate* (emphasis

added). Applicants submit that there is simply no suggestion in the combination of references to arrive at the present invention. The two references cited by the Examiner are both directed to the issue of trying to increase an immune response to an antigen, but each reference proposes an *entirely different method* to solve this problem, and neither reference teaches or suggests that one of skill in the art should look beyond the immediate solution in the reference to an entirely different solution. Moreover, as discussed below, there are reasons why the combination of references is incompatible with the solution offered by the present invention. Applicants submit that the combination of references, when viewed as a whole, does not render obvious the present invention.

More specifically, McKenzie et al. is directed to one means of increasing the immunogenicity of an antigen, which is by conjugating the antigen to a carbohydrate polymer comprising mannose. The teachings of McKenzie et al. are that this conjugation is *sufficient* to improve the immune response against the antigen. Indeed, McKenzie et al. teach that the direct administration of the conjugate stimulates cellular immunity, and so there is simply no reason provided in McKenzie to do anything further or to look to other types of vaccines. There is absolutely no teaching or suggestion in McKenzie et al. that it would be desirable to increase the immunogenicity of the *antigen conjugate*, nor specifically to pulse dendritic cells, or *any* antigen presenting cells, with the antigen conjugate *ex vivo*. this is because the antigen conjugate *is the means of increasing immunogenicity* of the antigen in McKenzie et al. Therefore, it is submitted that there is no basis in McKenzie et al. for the Examiner to conclude that one would want to take advantage of dendritic cells to increase the immunogenicity of the antigens described by McKenzie et al. Indeed, the only type of administration disclosed, exemplified or inferred in McKenzie et al. is direct injection or oral administration (see page 5, lines 18). Moreover, McKenzie et al. provides data showing that direct administration of the conjugate *in vivo* to mice and humans resulted in positive effects on an immune response and tumor burden. Given that McKenzie et al provide a complete solution to the problem of increasing an immune response to an antigen and do not in any way suggest *ex vivo* pulsing of any cells with the antigen, the only possible source of a suggestion or desirability to produce the combination of references and arrive at the present invention would have to come from Marakovsky et al.

Based on the December 20 interview, it seems to be the Examiner's position that by simply teaching the use of dendritic cell vaccines to enhance the presentation of antigens, Marakovsky et al. provides a sufficient reason to suggest the combination with the antigen conjugate taught by McKenzie et al. In the Office Action, the Examiner states that one of skill in the art would be motivated by the desire to take advantage of the dendritic cells to increase the immunogenicity of the antigen conjugate. However, Applicants submit that Marakovsky et al. provide a completely different solution to the problem of enhancing an immune response to an antigen than McKenzie et al., and that Marakovsky's solution is actually not compatible with the claimed invention or with advantages provided by the presently claimed invention. Therefore, the combination of McKenzie et al. and Marakovsky et al. will not be sufficient to arrive at the present invention.

More particularly, Marakovsky et al. teach a method to enhance the ability of dendritic cells to stimulate an immune response, and the specific *solution* proposed by Marakovsky et al. to the issue of enhancing an immune response to an antigen and particularly, to enhancing the ability of dendritic cells to stimulate an immune response, has *nothing* to do with how the antigen itself is provided to the cells. Rather, Marakovsky's solution requires the contacting of dendritic cells with CD40L *after* providing the dendritic cells with an antigen in order to activate the dendritic cells, and thus improve the ability of the dendritic cells to act as antigen presenting cells. The antigen in Marakovsky et al. is provided to the dendritic cell in one of two ways: by pulsing a dendritic cell with an antigen or by expressing the antigen recombinantly in the dendritic cell. Applicants initially note that with regard to the possibility of recombinantly expressing the antigen by the dendritic cell, the combination of Marakovsky et al. and McKenzie et al. are absolutely incompatible. It is not possible to recombinantly express the antigen conjugated to a carbohydrate polymer with fully oxidized mannose in a dendritic cell. With regard to the pulsing of the dendritic cell with antigen, it is clear from a reading of Marakovsky et al. that in no way does this reference envision anything other than an antigen that has been purified or partially purified, such as from tumor lysates, or produced recombinantly. There is no discussion of using any type of antigen conjugate nor any indication that Marakovsky et al. contemplates or appreciates that the selection of antigen would somehow change or further improve the immune response provided by the dendritic cells that have been activated with CD40L. Again, it is not the antigen that provides a basis for the invention in

Marakovsky et al.; it is the requirement for the use of CD40L to activate dendritic cells, which is completely different than the solution to enhancing immunogenicity provided by McKenzie et al., or the solution provided by the present invention. Applicants note that at least claims 86-90, which are product-by-process claims, would exclude a step of contacting the cells with CD40L after pulsing with antigen. It is also noted that there is no teaching or suggestion in Marakovsky to use any other antigen presenting cell than a dendritic cell. Therefore, there is no suggestion in Marakovsky et al. to modify the teachings of McKenzie et al. to arrive at the present invention, or *vice versa*.

Moreover, Applicants note that the composition of the present invention, because the antigen conjugate has the special characteristic of being delivered to the MHC Class I pathway of the APC, is able to preferentially elicit a cellular immune response, and in particular, a cytotoxic T lymphocyte (CTL) response, which has been demonstrated by the present specification. Claim 73 has been amended to emphasize this characteristic of the composition of the invention which is not present in, suggested, enabled or inferred by Marakovsky et al. To the contrary, Marakovsky et al. is not directed to anything other than purified or partially purified antigens or recombinant antigens, and in fact, teaches that antigens are classically processed and presented (see col. 11, lines 4-11). The experiments of Marakovsky are all directed to evaluating T cell proliferation, which is typically used to evaluate $CD4^+$ T cell activation, and Marakovsky et al. notes that CD40L and CD40 are important molecules in the elicitation of $CD4^+$ responses and B cell responses (see col. 6, lines 50-60). Marakovsky does not indicate any preference for inducing a CTL response and he does absolutely nothing to the dendritic cell to promote CTL responses. Marakovsky et al. only teaches a method to mature the dendritic cell, which would primarily enhance CD4+ responses and B cell responses for pulsed antigens, and as discussed above, expression of recombinant antigens in the dendritic cell is not compatible with the use of an antigen-carbohydrate polymer conjugate. In contrast, the present invention shows that processing of the recited antigen conjugate by APCs induces a more potent CTL response than APCs that have been pulsed with antigen alone, as is done in Marakovsky et al. (see Examples).

The Examiner seems to argue that one viewing both McKenzie et al. and Marakovsky et al. would simply decide to put the antigen conjugate of McKenzie et al. into the dendritic cell of Marakovsky et al., but Applicants submit that there is no basis for this in either disclosure nor any

motivation that would come from the art in general. Indeed, there is absolutely no reason that one reading Marakovsky et al. and McKenzie et al. would go to the extra effort and trouble of making and using the antigen-carbohydrate polymer conjugate described in McKenzie et al. to put into dendritic cells - (1) the teachings of Marakovsky et al. are that *CD40L* makes the dendritic cell a better antigen presenting cell, so that any conventional antigen is suitable and therefore, there is no need or any motivation at all to put effort into constructing a more complex antigen in view of these teachings; and (2) the teachings of McKenzie et al. do not indicate that there would be any reason to go to the trouble of putting the antigen conjugate into a dendritic cell and putting a patient through additional steps, because they have already shown that direct administration of the antigen conjugate is efficacious and boosts cellular immunity. The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. *In re Mills*, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990). Applicants submit that neither the combination nor the knowledge in the art at the time of the invention rises to this level.

Indeed, Applicants submit that it was not until the present invention that the significant advantages of the pulsing of dendritic cells with the recited antigen conjugate were realized, and without such realizations, there is simply no reason that one would have taken the conjugate out of a direct administration method, and there is simply no basis in the combination of references that could possible lead one of skill in the art to know or appreciate these advantages. More specifically, prior to the time of the presently claimed invention, as discussed in the specification (*e.g.*, see page 41, line 18 to page 42, line 20), it was not known that administration of the recited antigen conjugate alone could be impacted by the presence of naturally occurring antibodies against the tumor antigen. However, it was discovered that naturally occurring antibodies can cross-react with many tumor antigens, and when this happens, the conjugate is diverted by Fc receptor uptake of the antibody, and the desired input of the conjugate into the class I MHC pathway, and thus the enhancement of cellular immunity provided by the conjugate, is diminished. Without this appreciation, there would have been absolutely no reason to look to the use of *ex vivo* pulsing of APCs (including dendritic cells) to effectively put the conjugate into the class I pathway and also to "hide" the conjugate from

the natural humoral immune response. McKenzie et al. is clearly not aware of or concerned about this issue and the issue is irrelevant to Marakovsky et al.

Moreover, the inventors have further discovered that the provision of the antigen conjugate to APCs has the particularly attractive and unexpected advantages of: (1) causing the dendritic cell to mature (become activated) in the absence of any exogenous factors (*e.g.*, CD40L is not required at all); and (2) causing the antigen to preferentially become processed via the class I pathway (*i.e.*, primes CTL responses), in addition to the class II pathway, thus enhancing cellular immune responses against the antigen (*i.e.*, which is different than the "classical processing and presentation" of Marakovsky et al.). Indeed, as discussed above, the present specification shows that processing of the antigen conjugate by APCs induces a more potent CTL response than APCs that have been pulsed with antigen alone, as is done in Marakovsky et al. McKenzie et al. does not teach or suggest the advantage of causing a dendritic cell to mature, since there is no teaching of *ex vivo* pulsing in McKenzie et al. and Marakovsky et al. use a completely different means to mature the dendritic cell (CD40L), thus removing any need to look to another solution. With regard to the enhancement of cellular immunity, from the viewpoint of McKenzie et al., the direct administration of the conjugate was already effective in inducing cellular immunity (*e.g.*, the studies in McKenzie et al. did not reveal that if natural antibody responses were blocked, the efficacy of the conjugate would be increased), and Marakovsky et al. *could not* teach or suggest these advantages because the method of Marakovsky et al. does not modify the antigen presentation by the cell (*i.e.*, as taught in Marakovsky et al. in col. 11, the antigens are classically processed and presented), and the CD40L of Marakovsky et al. only cause the dendritic cell to become a better antigen presenting cell for primarily $CD4^+$ and B cell responses when the dendritic cell is pulsed with the antigen.

Finally, Applicants submit that, given the deficiencies of the teachings of McKenzie et al. and Marakovsky et al. with regard to the claimed invention, one of skill in the art viewing the combination of references would have absolutely no expectation that the method of Marakovsky et al. would improve the immune response elicited by the conjugate of McKenzie et al., noting that McKenzie et al. already provide a solution to providing the antigen alone. It was not possible to predict the particular effects of the conjugate on the dendritic cell maturation, and it is Applicants position that one could not predict that the combination would provide an advantage over the specific

immune response-enhancing solution of McKenzie et al. alone or the completely different immune response-enhancing solution of Marakovsky et al. alone. Accordingly, Applicants submit that the combination of references cited by the Examiner fails to make obvious the present invention.

In view of the foregoing discussion, the Examiner is respectfully requested to withdraw the rejection of Claims 1, 3-11, 13-17, 19-21, 24-26, 38 and 70 under 35 U.S.C. § 103.

Applicants have attempted to address all of the Examiner's concerns as set forth in the August 12 Office Action and submit that the claims are in a condition for allowance. Any additional questions or concerns regarding the claims or Applicants' position should be directed to the below-named agent at (303) 863-9700.

Respectfully submitted,

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